AUTISM

AND THE ENVIRONMENT

New ideas for advancing the science

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NIEHS Keystone Campus

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In partnership with

AUTISM SPEAKS™
It's time to listen.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Meeting Structure

- Four subtopics
  - What have we learned from other disorders?
  - Novel tools and approaches in genomics and toxicology
  - Cellular and molecular mechanisms
  - Exposure science and epidemiology
- Expectations
  - All encouraged to participate in discussion
  - Recognize value of diverse backgrounds and viewpoints
  - Cross cutting themes likely to emerge

Charge to group

- Be bold and forward thinking
  - Don't be constrained by cost
  - Think about next 5-10 years
- Consider mix of approaches (big and small; short and long term)
- Consider multidisciplinary/interdisciplinary needs and opportunities

Assumptions

- Autism is complex, involves many genes, many different exposures
- Relevant genetic susceptibilities and exposures are likely to vary among individuals
- Environment is defined broadly
  - Industrial, agricultural chemicals
  - Endocrine active compounds
  - Pharmaceuticals, medical exposures
  - Lifestyle, nutrition, social environment

Overarching questions

- What are the primary obstacles to progress?
- What are the best opportunities/questions/areas of science to pursue?
- What are the best mechanisms to achieve progress?

Topic 1: Lessons learned from other disorders

- How has information about known risks from single genes or pathways provided clues for environmental etiologies?
- What are the most successful examples of interdisciplinary integration of basic and clinical research?
- What is needed to shift current paradigm of waiting for epidemiology to provide clues to pursue in mechanistic studies?

Topic 1: Lessons learned from other disorders

Points to consider

- There is value in considering relation of environmental risks to both broad and narrow disease phenotypes.
  - Focus on neural pathways controlling discrete domains of functioning, need to better describe and define clinical subtypes
  - Examine genes that control many areas of functioning and think broadly in terms of phenotypes.
- Information about disease mechanisms is critical for generating hypotheses
  - Good precedence for environmental and genetic risks converging on same pathways (e.g., alpha synuclein and pesticides in Parkinson's)
  - Think beyond metabolic enzymes as targets for environmental exposures
- Sustained back and forth exchange between basic and clinical science helpful, but difficult to achieve in traditional R01

Topic 1: Lessons learned from other disorders

Points to consider

- A range of epidemiologic approaches is needed to offset weaknesses of any one approach
  - Need to collect better, more timely exposure information
  - Environmental exposure data may explain differences in genetic findings
- As international surveillance infrastructure improves, there will be opportunities for using contrasts based on geography, lifestyle, nutrition
- Large populations are needed
  - May require combining studies, harmonization of methods
- Greater attention to environmental etiologies of disease can arise from
  - Clinical cases arising from unusual and/or high level exposures
  - Clear examples of gene x environment interplay
  - Changes in prevalence and increased public interest

Topic 2: New tools and approaches in genomics and toxicology

- How can new tools and approaches be used to advance research in environmental contributors to autism?
  - Bioinformatics and computational approaches
  - Novel sequencing methods, epigenetic approaches
  - Induced pluripotent stem cells (iPSCs)
  - High throughput screening approaches

Topic 2: New tools and approaches in genomics and toxicology

Points to consider

- How to approach genetic complexity of autism
  - Contribution of rare copy number variants (CNVs) vs. common variants
    - Rare variants are often highly penetrant, common variants may confer lesser risk
  - Lack of specificity between gene variation and clinical condition.
    - Variation in SHANK3 may increase risk of multiple disorders, specificity depends on other genes, exposures
  - Most genetic studies are conducted with stringent cases, not representative of general population of autism
- How to correlate mechanism at gene expression level to genotype
- How to translate human phenotype to cellular phenotype

Topic 2: New tools and approaches in genomics and toxicology

Points to consider

- Recent genetic findings provide many clues to pursue
  - Good agreement on a number of genes related to autism
  - Ongoing studies (e.g., exome sequencing) will generate more clues in near future
- A range of models should be considered
  - Use of convergent pathways for screening
  - Many knock out models available, although these have limitations
  - Differentiated cellular systems could be used to address synapse formation, connectivity
  - iPSCs could be used to advantage (e.g., fibroblasts from patients with defined phenotypes)
- Bioinformatics approaches can be used to define potential relationship between genes and exposures
  - National Toxicology Program example with exposures linked to diabetes and obesity

Topic 3: Cellular and molecular mechanisms toxicology

- How can advances in autism science inform mechanistic investigations?
  - Genetic findings
  - Immune findings
- What models are available and most relevant?
- How can we more effectively develop, disseminate and use model systems?

Topic 3: Cellular and molecular mechanisms toxicology

Points to consider

- Cellular models of the nervous system often lack key components – the neuro-immune interactions. Future models should incorporate one or more aspects of neuro-immune interactions.
  - Simpler models (e.g. dissociated neurons) are not necessarily better
  - Organotypic cultures may address some, but not all, of these issues.
    - Permit studies that focus on how dendritic growth, synapse formation and pruning are influenced by xenobiotics.
  - Incorporate cytokine profiles found in ASD to in vitro models
  - Need links to in vitro toxicity data (e.g., Tox-21).
  - Need to understand anatomical correlates of functional impairments.
  - Use a tiered approach: molecular -> cellular -> organotypic -> in vivo.

Topic 3: Cellular and molecular mechanisms toxicology

Points to consider

- Develop iPSC or mSC lines from individual patients with syndromic and idiopathic autism that have deep phenotyping.
  - These approaches may preserve the genetic complexity that confer autism risk and provide novel opportunities to study neurodevelopmental impairments relevant to ASD.
- Develop targeted mice that express several disrupted genes relevant to autism.
  - Develop mice with CNVs within high risks regions.
  - Take advantage of mild phenotypes to study additive (synergistic) influence of xenobiotics.
- Study toxicants such as BPAs, PBDEs that disrupt hormonal systems and their relationship to behavioral outcomes in social behavior and anxiety.
- Study whether exposures influence parental imprinting and their consequence on epigenetic changes in the subsequent generations.

Topic 4: Exposures science and epidemiology

- How can we harness improvements in exposure metrics?
- What study designs and analytic approaches are best suited for g x e?
- Are there unique international opportunities?

Topic 4: Exposures science and epidemiology

Points to consider

- Time-varying exposure problem
  - Environment is time dependent, genetics is not
  - What does this imply for type of samples? Study design?
  - Developmental approaches are critical, prospective approach is ideal
  - What is pragmatic?
- How to strategically collect samples and data in such a way that does not constrain our ability to look at a variety of exposures?
  - Do time series
  - Discovery mode rather than measuring specific identified exposures
  - Learn from proteomics, metabolomics – analyze spectrum of peaks

Topic 4: Exposures science and epidemiology

Points to consider

- New data collection strategies
  - Passive monitoring technologies – participant wears badge, dermal patch
  - Collect diapers and store them
  - New technologies like cell phones to capture real-time exposure info
  - New technologies being developed under NIH Genes Environment and Health Initiative
  - Develop website/portal about new technologies to provide information to researchers (e.g., PHEN-X Project – NIH funded project that puts information about technology on the internet)
- Need better methods to capture and analyze dietary exposures, mixtures, cumulative effects

Topic 4: Exposures science and epidemiology

Points to consider

- Emerging areas
  - Genes involved in metabolism of xenobiotics
  - Maternal genetic profile and environmental exposures
  - Early childhood exposure of mom – second and third generational effects, latent effects of early exposures to mother, grandmother
  - Statistical tools to help with incorporating environmental exposures into autism studies
  - Get statisticians involved early on in study design
- Novel study populations
  - China – large ongoing studies looking at women of reproductive age
  - Famine, heavy toxicant exposures, drought
  - NCI studies of women with good exposure measurements, add on autism piece
  - NCS produced document to recommend how to add autism piece
  - To capitalize on ongoing studies, international opportunities, need to overcome barrier of making a good ASD diagnosis – use endophenotype tools (e.g., SRS, self-administered tools) to establish autism diagnosis more quickly and cost-efficiently

Topic 1: Summary of recommendations

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Topic 2: Summary of recommendations

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Topic 3: Summary of recommendations

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Topic 4: Summary of recommendations

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Next steps

- Create meeting report
- Post on NIEHS and Autism Speaks websites
- Report to Interagency Autism Coordinating Committee (IACC)
- Consider recommendations for development of future initiatives and activities

Opportunities for public comment to IACC

- The IACC's primary mission is to facilitate the efficient and effective exchange of information on autism activities among the member agencies, and to coordinate autism-related programs and initiatives.
- Develops and annually updates a strategic plan for the conduct of, and support for, autism spectrum disorder research
- Additional information about the IACC, including opportunities for public comment, can be found at http://iacc.hhs.gov/

Thank you

- Meeting participants and webcast viewers
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